PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PN0398-PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/NO2004/000392	International filing date *(day/month/year)* 17.12.2004	Priority date *(day/month/year)* 18.12.2003

International Patent Classification (IPC) or national classification and IPC
A61K49/00

Applicant
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1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10.10.2005	11.11.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NO2004/000392

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-32 as originally filed

   Claims, Numbers

   1-13 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 10-13 (IA)

because:

☒ the said international application, or the said claims Nos. 10-13 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 10-13 (IA)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NO2004/000392

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4
	No:	Claims	1-3,5-13
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. Re Item III.

Claims 10-13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(l) PCT).

2. Re Item V

The following document have been cited in the search report. Where reference is made to them, the following numbering is used; unless otherwise indicated, reference is made to the relevant passages indicated in the Search Report:

Dl: US 2001/055566 Al (LUIKEN, M.D. GEORGEA ETAL) 27 December 2001
D2: WO 00/61194 A (INST1TUT FUER DIAGNOSIIKFORSCHUNG 19 October 2000
D3: EP-A-1 170 021 (SHERING AKTIENGESELLSCHAFT) 9 January 2002
D4: WO 0191805 A (BRACCO RESEARCH USA;) 6 December 2001
D5: WO 98/47541 A (NYCOMED IMAGING) 29 October 1998
D6: MARCHI-ARTZNER, VALERIE El AL: "Adhesion of Arg-Gly-Asp (RGD) Peptide Vesicles onto an Integrin Surface: Visualization of the Segregation of RGD Ligands into the Adhesion Plaques by Fluorescence' LANGMUIR, 19(3), 835-841 February 2003(2003-02), XP002326372
D7: EP-A-0 800 831 (OAIICHI PURE CHEMICALS CO. LID;) 15 October 1997
D8: WO 00/71162 A(MAILINCKRODT INC) 36 November 2000
D9: ACHILEFU S El AL: NOVEL RECEPTOR-TARGETED FLUORESCENT CONTRAST AGENTS FOR IN VIVO TUMOR IMAGING' INVESTIGATIVE RADIOLOGY, PHILADELPHIA, PA, US, vol 35, no.8,2006, pages 479-485,XP000978923
D10: WEINER RONALDE El AL: Radiolabeled peptides for the diagnosis and therapy of oncological diseases' APPLIED RADIATION AND ISOTOPES" NOV2002, vol. 57, no.5, November 2002, pages 749-763, XP002326772
D11: DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; June 2003, TIAN FENG Feng et AL: Overexpression of COX-2 and its clinical significance in non-small lung cancer XP002326773 Database accession no. NLM12895344
D12: DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; 26 July 2001, KAJITA T et AL: The expression of vascular endothelial growth factor C and its receptors in can-small cell lung cancer."XP002326774 Database accession no. NLM1 1461086
D13: WO 2005/002293 A (VANDERBILT UNIVERSITY) 6 January 2005
014: W02005030266A (AMERSHPM HEALTH AS;) 7 April 2005
D15: WOO1/89584 A(NYCOMED IMAGING) 29 November 2001
D16: WO2005019247A (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS) 3 March 2005

D17: WO2005003166

2.1 Novelty (Art.33(2) PCT)

Dl (US2001/055566) discloses conjugates comprising a somatostatin peptide, (a targeting hormone for lung cancer according to the present application, see page 6, line 22) and a fluorescent agent. Use as in vivo imaging agent for lung cancer is also disclosed. This document is prejudicial for the novelty of claims 1-3, 6-13.

D2 (WO 00/61194) and **D3** disclose optical imaging agents comprising a contrast agent made of a fluorescent dye conjugated with a somatostatin peptide as tumor targeting moiety (a targeting moiety for lung cancer according to page 6, line 22 of the present application). D2 also states that the low molecular weight of the conjugate improves the pharmacodynamic properties of the diagnostic agent and decreases the immunogenic responses. The use for diagnosis of cancer of the bronchial tract is also claimed. These documents are prejudicial for the novelty of claims 1-3, 6-13.

D4 (WO 01/91805) discloses optical imaging agents for the in-vivo optical imaging of cancer comprising a vector moiety being a peptide targeted to NP-1 (NP-1 is a type of VEGF receptor) conjugated to a detectable fluorescent moiety. Since the VEGF receptor is one of the targets for lung cancer according to the present application (see claim 5), this document is novelty destroying for the compound claims 1-3,5-8.

D3 (WO 98/47541) discloses optical imaging agents comprising a vector moiety being an organic moiety or a peptide moiety, (one of the preferred vectors being targeted to the VEGF receptor) and a detectable moiety (preferred is a fluorescent moiety). Since the VEGF receptor is one of the preferred targets according to the present application, this document is novelty destroying for the compound claims 1-3,6-8.

D4 (XP002326372) discloses the preparation of conjugates between RGD peptides, which according to the description of the application (see example 7) are suitable to target lung cancer, conjugated to a fluorescence probe. Use for imaging of cancer is disclosed. The compounds disclosed in this document therefore fall in the definition of claims 1-3,5-7.

D5 (EP 0800831) discloses optical imaging contrast agents comprising a conjugate between a vector moiety (preferred are antibodies) and a fluorescent group. Since targeting to the p53 protein is disclosed, (p53 is mentioned as a target for lung cancer in the description of the present application at page 5, line 28), this document is prejudicial for the novelty of claims 1,3.

D8, (WO 00/71162) discloses optical imaging agents comprising a fluorescent dye conjugated with a peptide of low molecular weight having affinity for cancer cells. A preferred targeting agent is bombesin, which according to the present application is also suitable to target lung cancer (page 6, line 32). D6 also states that the low molecular weight of the conjugate enhances fluorescence efficiency for imaging purposes. This document is prejudicial for the novelty of claims 1-3,6-8.

2.2 **Inventive step (Art.33(3) PCT)**

The problem underlying the present application is the provision of contrast agents for the optical imaging of lung cancer. As a solution the inventors propose agents which can be detected by means of optical imaging and which have a preferential affinity for lung cancer cells. Preferred are imaging agents having a molecular weight below 14000 Daltons, Furthermore, the preferred imaging agents comprise a targeting moiety conjugated to a reporter moiety. A list of reporter moieties is given in claim 5, and others are listed in the description of the application. As already indicated above, a large part of the subject matter claimed in the present application is not new over the prior art. The subject matter which is still new differs from the prior art in that specific targeting moieties not present in the imaging agents of the prior art have been selected.

D2, **D8** and **D9** disclose the rationale of preparing optical imaging agents made of a fluorescent dye conjugated with a peptide of low molecular weight having affinity for specific tumor types. These documents disclose the advantages of preparing low molecular weight conjugates to improve the pharmacodynamic properties of the contrast agents, to decrease the immunogenic responses and to enhance fluorescence efficiency.
Even if these documents do not specifically mention the imaging of lung cancer, their teaching indicates that at the date of filing of the present application, the skilled person knew how to

prepare optical imaging contrast agents targeted to specific cancer types, how to select the proper reporter moieties, the targeting moieties and how to conjugate them together.
For this reason, it appears that, confronted with the problem to prepare imaging agents to image lung cancer the skilled person would have selected the targeting moieties which are listed in claim 5. These in fact appear to be known targeting moieties which have already been used to transport imaging agents to lung cancer (see D10-D12).
For this reason the subject matter underlying the application which is new does not appear to involve an inventive step in the sense of Art.33(3) PCT.

It is also to be observed that, even if the applicants have provided some explicit examples reporting the synthesis of some preferred imaging agents according to the invention, they have not provided any evidence showing that any of these compounds is suitable to image lung cancer, It is therefore not clear whether the problem underlying the application has been solved.

2.3 Industrial application (Art.33(4) PCT)

For the assessment of the present claims 10-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3. Re Item VI.

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*

WO 2005/002293	6 January 2005	25 June 2004	25 June 2003
W02005030266	7 April 2005	28-09-2004	29-09-2003
W020050119247	3 March 2005	13 August 2004	13 August 2003
W02005003166	13 January 2005	7 July 2004	8 July 2003

4. Re Item VIII.

Claims 1-4 appear to define the invention as a result to be achieved and to merely claim the underlying technical problem. As such these claims are not considered clear.
Also, some expressions are not clearly defined, rendering unclear the scope of protection of the claimed subject matter: for example: "contrast agent substrate" and "contrast agent product" in claim 4, "fat-related compound" and "traditional organic drug - like small molecules" in claim 6.